further identification of the pigment found in the liver cells.

SUMMARY AND CONCLUSIONS

A case of the recently described clinico-pathological entity "chronic intermittent jaundice with unidentified pigment in liver cells" is presented.

The clinical picture and laboratory findings are outlined and emphasis is laid on the characteristic findings revealed by liver biopsy. It is noted that the syndrome can be separated from other cases of jaundice.

Features of the differential diagnosis are discussed. The course of the condition is benign, the prognosis good and the exact etiology obscure.

We wish to thank Dr. L. A. Caswell who kindly referred this case to us and St. Bartholomew's Hospital who forwarded their case summary. We are also indebted to Dr. W. H. Mathews of our Pathology Department for his work in interpreting the tissue sections.

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SEVERE SENSITIVITY REACTION (HEPATITIS, DERMATITIS AND PYREXIA) ATTRIBUTABLE TO PHENYLINDANEDIONE*

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THE VALUE of anticoagulant therapy in thromboembolic disease is now well established, but unfortunately the ideal anticoagulant has not yet been found. There are available a number of potent oral anticoagulant drugs which, by reducing prothrombin activity, successfully prevent thrombosis. However, undesirable side effects in the form of hæmorrhage or, less commonly, in the form of systemic reactions, may occur. Such reactions may constitute a greater danger to the patient than the disease for which the anticoagulant drug is being given.

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Of the oral anticoagulants in general use, we have found phenylindanedione (PID, phenindione, Danilone or Hedulin) to be most satisfactory.[1, 2] Because of the rapidity of onset of its effect, constancy of response in a given patient, freedom from hæmorrhagic and other complications, and response to antidote (vitamin K_1), it has recently been described as the drug of choice.[3-6] As it is likely that PID (phenylindanedione) will be used increasingly, it is considered desirable to report an instance of unusual sensitivity reaction observed to follow its administration.

The action of the coumarins and of the indanediones is to produce "hypoprothrombinæmia" by interfering with the ability of the liver to synthesize Factor VII and prothrombin. In view of this probable mode of action, it might be expected that toxic hepatic reactions would be common. Such has not proven to be the case. Wright, Marple and Beck[7] refer to an exaggerated response to dicoumarol in a patient with gross liver enlargement. They also state[8] that the effects of dicoumarol are unpredictable in the presence of hepatic dysfunction. For this reason, Barker[9] states that definite hepatic disease is a contraindication to the use of dicoumarol.

A survey of the literature reveals only one report of toxic hepatitis due to oral anticoagulants. Makous and VanderVeer[10] observed a severe sensitivity reaction with hepatitis, dermatitis, pyrexia, anæmia and leukæmoid blood picture in a patient treated with PID. A similar instance is here reported.

A 64-year-old white man was admitted to the Winnipeg General Hospital on May 4, 1955, with a three-day history of severe lower sternal and epigastric pain when walking. The pain came on after walking half a city block and disappeared after he rested for a few minutes. His past history included the passing of a renal calculus in 1934, repair of a right inguinal hernia in 1951, and in 1954 a diagnosis of gout for which no treatment was given. Physical examination on admission showed him to be moderately obese with a plethoric complexion. The heart sounds were normal, the blood pressure 165/95. There was no evidence of congestive heart failure. Abdominal examination was negative. The spleen was not palpable and there was no lymphadenopathy. An electrocardiogram showed terminal T wave inversion in V_3, V_4 and V_5 precordial leads. This was not present in a previous tracing in March 1954. Urinalysis and chest radiograph were negative. Examination of blood was as follows: hæmoglobin, 17.5 g. % (112%); red cell

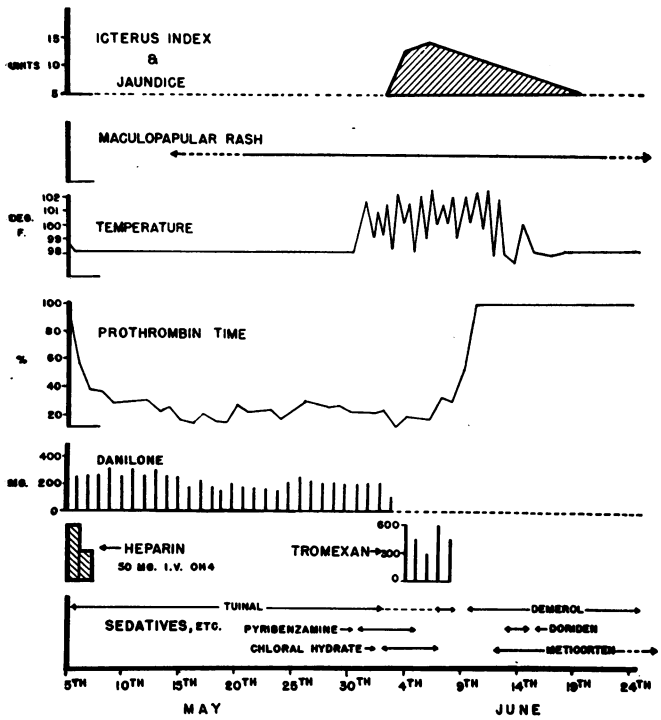

Fig. 1.—Hepatitis, dermatitis and fever attributable to phenylindanedione.

count, 6 million/c.mm.; white cell count, 10,500; differential count: neutrophils 54%, eosinophils 5%, lymphocytes 32%, monocytes 3%, atypical 4%; sedimentation rate 17 mm. per hour; icterus index, 5 units; prothrombin time 13.5 sec. (100%).

A diagnosis of angina pectoris with impending myocardial infarction was made and the patient was put at bed rest and given heparin, 50 mg. intravenously every 4 hours for 6 doses. Phenylindanedione (PID), 500 mg. in divided doses, was given the first day. The following day the patient had an episode of retrosternal pain with shortness of breath which was relieved with the sublingual use of 1/200 grain of nitroglycerin. On the third day a few fine rales were noted at both lung bases. The blood pressure varied during the first five days from 135/90 to 170/120. Serial electrocardiograms on May 5 and May 12 showed a lower T wave in lead I, inversion of T in AVL and increased inversion of T waves in V_2, V_3, V_4 and V_5. There were no QRS changes indicative of myocardial infarction.

For the first two weeks the patient had occasional attacks of chest pain which responded to nitroglycerin. The prothrombin time was maintained at between 25 sec. (36%) and 58.5 sec. (14%), with daily doses of PID averaging 223 mg. per day (Fig. 1).

On the 15th day a diffuse, itchy, erythematous macular eruption developed on the patient's back and upper abdomen (Fig. 2). This rapidly became generalized to involve the face and extremities as well. The intense pruritus did not respond to local applications or to drugs of the antihistamine group and continued unabated for the subsequent three weeks. The rash was diagnosed as dermatitis medicamentosa and barbiturate sedation was discontinued, but without effect on the pruritus or the eruption. Twenty-seven days after admission, 12 days after the onset of the rash, fever was noted for the first time, and on the 30th day, clinical jaundice was first seen. The liver margin became palpable 4 cm. below the right costal margin and was firm and non-tender. A maximum icterus index of 15 units was reported three days after the onset of jaundice. White cell count at this time was 8500 with 36% mature neutrophils, 21% young forms, 5% eosinophils, 2% basophils, 24% lymphocytes, 3% monocytes and 7% atypical lymphocytes. The erythrocyte sedimentation rate rose to 60 mm. per hour (previous maximum 38 mm.). The alkaline phosphatase was 19.2 King units. The cephalin flocculation was +++, thymol turbidity ++ and thymol flocculation 4 units. A stool specimen collected at this time proved negative for virus. Three weeks after the onset of jaundice the sedimentation rate was 40 mm. per hour, icterus index 5 units, white cell count 11,500 with no significant change in differential cell types, the Quick one-stage prothrombin time 15 sec. (90%); the absolute values of prothrombin and Factor VII (one-stage technique) were within normal limits. Factor V assay (one stage) was 40% of normal; this rose to 100% of normal two weeks later.

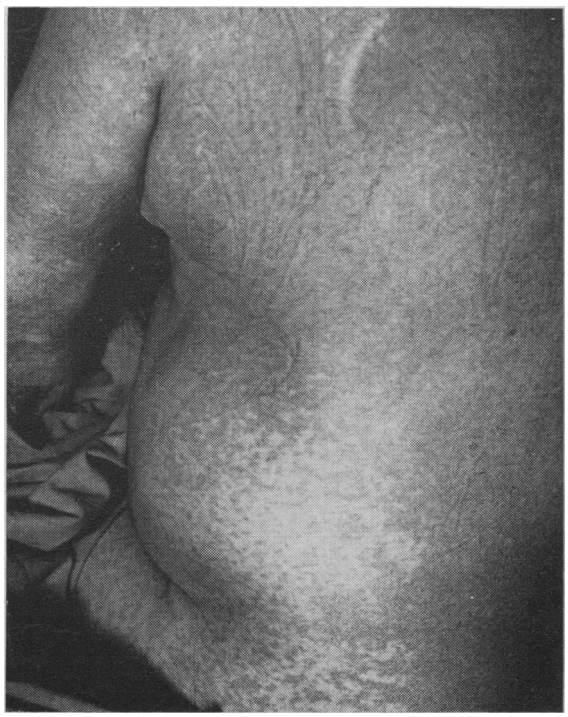

Fig. 2.—Erythematous macular eruption which appeared after administration of Danilone for 15 days.

On the 28th day of admission, 13 days after the onset of the rash, PID was discontinued and Tromexan substituted as an anticoagulant for five days and then it was also discontinued. The prothrombin time returned to normal within 48 hours. Jaundice, anorexia, rash and fever persisted unabated until the 39th day of hospitalization although the patient did not appear seriously ill. By this time the rash had been present for 24 days, daily afternoon fever to 102.5° F. for 12 days and jaundice for 9 days (Fig. 1). Meticorten (prednisone), 5 mg. t.i.d., was given orally, with improvement beginning the following day. A week later the rash had cleared completely and the liver margin was barely palpable. The patient's temperature remained normal after three days of Meticorten therapy. The subsequent course was uneventful and the patient was discharged on the 49th day. Meticorten was continued for 10 days after discharge, a total of three weeks, since considerable pruritus recurred when the dose was reduced before this.

DISCUSSION

There have been few reports of major or serious toxic reactions to PID in the literature and the incidence of these reactions certainly appears to be very low. Hæmorrhagic complications are considered to be due to overdosage or misuse of the drug or to a co-existent organic disease which has been ignored or unsuspected. Townsend *et al.*[11] report one patient who developed stomatitis and granulocytopenia while taking PID, with prompt recovery on withdrawal of the drug. MacMillan and Brown[12] noted two patients with agranulocytosis possibly due to PID, and Kirkeby[13] reports a case of agranulocytosis in which there was also a pruritic drug rash. The rash and blood picture improved dramatically with the use of cortisone although the patient died approximately three weeks later in uræmia, without definite cause of the latter being found.

This patient almost certainly suffered a severe sensitivity reaction. The consecutive development of a typical pruritic drug rash, with fever, anorexia and jaundice, strongly suggests a drug sensitivity. The rapid response of all symptoms and signs to Meticorten also favours this diagnosis. The only drug other than PID which could possibly be incriminated is the Tuinal (sodium secobarbital and amobarbital) given for sedation during the first 28 days in hospital. However, the patient had previously taken barbiturates without reaction and has subsequently taken them without untoward effect. In view of the history, course and laboratory evidence, other types of jaundice need not be considered.

In the only case report of toxic hepatitis due to PID found in the literature,[10] the reaction was very similar to that in the patient here described, but was more severe. This difference may have been due to the administration in their case of a second course of PID after the original reaction, at which time a leukæmoid reaction and anæmia also developed. The reaction in their case did not appear to respond as dramatically to corticotropin as did ours to prednisone.

Alexander[14] states that the drugs most frequently causing hypersensitivity hepatitis are the gold salts, phenurone and quinacrine, but others such as barbiturates, sulfonamides, and testosterone may do so. Clinical jaundice, with depressed hepatic function, is present but occasionally more serious hepatic necrosis may occur. According to Alexander, fever and skin eruptions commonly accompany the hepatitis, and immediate withdrawal of the offending drug is most important.

SUMMARY

A case history is presented of a toxic drug reaction to phenylindanedione. The patient developed, in order, pruritic rash, fever, hepatitis with jaundice. The rash was present for 12 days before fever developed; jaundice was apparent three days later and persisted for nine days. All the manifestations of hypersensitivity responded promptly to prednisone in small doses, although it was necessary to continue treatment for three weeks to prevent the recurrence of pruritus. References to other reports of toxic reactions to PID are discussed and the comparative rarity of these reactions is noted.

The authors are indebted to Dr. L. G. Israels and Dr. J. C. Wilt for hæmatological and virus studies on this patient.

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